UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/804,481	03/12/2001	David de Graaf	WIBL-P01-523	1227

28120 7590 01/10/2006

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 01/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/804,481	GRAAF ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-35,37-46 and 48-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-35,37-46 and 48-51* is/are rejected.

7)☒ Claim(s) *49 and 50* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed October 5, 2005 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Status of the Claims

3. Claims 32-35, 37-46 and 48-51 were amended. Applicants amended claims 32, 37 and 42. No claims were added or canceled. Therefore, claims 32-35, 37-46 and 48-51 are pending and examined on the merits.

Withdrawn Objections/Rejections

4. The rejection under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicants' arguments and/or amendments. The Noonberg et al. rejection under 35 U.S.C. § 102(b) is withdrawn in view of Applicants' amendments and/or arguments. The Noonberg et al. rejections under 35 U.S.C. § 103(a) are withdrawn in view of Applicants' arguments and/or amendments. The New Matter rejection under 35 U.S.C. 112, first paragraph is withdrawn in view of Applicants' amendments and/or arguments. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 112

5. Claims 32-35, 37-46 and 48-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicants' claims are directed to a broad genus recombinant vectors (e.g., viral, plasmid, etc.) that can infect host cells of any type (e.g., human, bacterial, yeast, etc.) via any mechanism (e.g., replicate, integrate, etc.). In addition, although said vectors must contain one or more recognition sites for a restriction enzyme, no limitation is placed on the type of restriction enzyme that may be used (e.g., class I, class II, class IIs, etc.).

In contrast, Applicants' specification provides only one example of a pSP-luc+ plasmid contains U1 and a Bae1 "double cleavage" restriction site i.e., a Bae1/U1 construct (e.g., see figure 4; see also Example on pages 21-23).

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the claimed invention (e.g., see *In re Edwards*, 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978); see also see also *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 (CAFC 1991)). The "written description" requirement may be satisfied by using "such descriptive means as words, structures, figures, diagrams formulas, etc., that fully set forth the claimed invention" (e.g., see *Lockwood*, 107 F.3d at 1572, 41 USPQ2d

at 1966). Furthermore, adequate disclosure, like enablement, requires representative species, which provide reasonable assurance to one skilled in the art that that applicant had possession of the ***full scope*** of the claimed invention (e.g., see *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure). In addition, when there is *substantial variation within the genus*, one must describe a sufficient variety of species to reflect the variation within the genus (e.g., see MPEP § 2163.05; see also see *In re Fisher*, 166 USPQ 18 (CCPA 1970)) ("… what the Applicants have actually made and tested [must] reasonably correlate with the scope of the amended claims").

In the present case, Applicants' specification discloses only one example of the claimed genus of recombinant vectors, the Bae1/U1 construct, which is not "representative" of this enormous genus (see above). For example, Applicants fail list representative recombinant vectors (e.g., viral, plasmid, etc.) that can infect representative host cells (e.g., human, bacterial, yeast, etc.) or any representative species of mechanism (e.g., replicate, integrate, etc.). In addition, the specification fails to provide support for the use of "single cleavage" restriction sites or "more than one" recognition sites (e.g., no "single cleavage" species are listed). Furthermore, a person of skill in the art would not expect a "single cleavage" enzyme to excise a restriction fragment that includes the recognition site especially if that enzyme cleaves within its own recognition site (e.g., many enzymes like BamHI, which cleaves G↓GATCC see below, would destroy the recognition site). Although the specificity of a restriction

enzyme may be changed by mutation and/or judicious selection of reaction conditions (e.g., see George et al., abstract wherein the recognition of BamHI could be "relaxed" by altering the reaction conditions; see also Lanio et al., Table I wherein mutations in EcoRV caused changes in the substrate specificity), no such "relaxation" has been described in Applicants' specification, nor has an alternative procedures (e.g., mutation) been suggested that might otherwise alter the enzymes recognition and/or cleavage sites. Moreover, it is unclear how multiple recognition sites can produce "a "single restriction fragment. Ten BaeI recognition sites, for instance, would produce twenty cuts in the modified nucleotide sequence (dual cleavage enzyme), which would lead to twenty fragments. Thus, it would appear that even for Applicants' most preferred embodiment (i.e., BaeI), only "one" recognition site could be used to produce the single restriction fragment (see 35 U.S.C. 112, second paragraph rejection below).

Thus, applicants have not demonstrated in "full, clear, concise, and exact terms" that they are in possession of the claimed invention especially with regard to sequences that do not possess a restriction site that can be "double cleavage" restriction site. It is well settled that claiming only a result (e.g., digestion with a single enzyme that excises a restriction fragment which includes a single recognition site and forms insertion sites in said nucleotide sequence) fails to satisfy the constitutional requisite of promoting the progress of science and the useful arts since this seeks to monopolize all possible ways to achieve a given result, far beyond those means actually discovered or contemplated by the inventor, so that others would have no incentive thereafter to explore a field already fully dominated. *O'Reilly v. Morse*, 15 How. 62, *In re Fuetterer*, 50 CCPA 1453, 1963

C.D. 620, 795 O.G. 783, 319 F.2d 259, 138 USPQ 217 ; *Siegel v. Watson*, 105 U.S. Appl.

D.C. 344, 1959 C.D. 107, 742 O.G 863, 267 F.2d 621, 121 USPQ 119.

Response

6. Applicant's arguments directed to the above written description rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "… that where, as in this case, (1) the inventive portion of the subject mater is disclosed and (2) any additional variability within the genus arises due to additional elements that are not part of the inventor's contribution, and when the level of knowledge and skill in the art would allow one skilled in the art to recognize that applicant was in possession of the genus, the written description cannot be deemed defective" (e.g., see 10/5/05 Response, page 5, last full paragraph).

[2] Applicants reiterate the arguments of record and contend that the claimed subject matter is described sufficiently … The factors which should be considered include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a know or disclosed correlation between structure and function, and the method of making he claimed invention … The specification provides a detailed description of the features of the claimed vector …. [including a definitions for the term vector and snRNA as cited in the specification at pages 10 and 15] … [and] the number of

claimed nucleic acid sequences as amended is not overly large because the restriction enzyme belongs to a unique family of restriction endonucleases that excise a fragment containing the recognition site" (e.g., see 10/5/05 Response, pages 6 and 7).

[3] Applicants argue, "... independent claims 32 and 42 have been amended to recite a 'recognition site' for a restriction enzyme ... ." (e.g., see 10/5/05 Response, page 7).

This is not found persuasive for the following reasons:

[1] The Examiner contends (1) that the inventive portion of the subject matte has not been disclosed and (2) any additional variability within the genus does not arise due to additional elements that are not part of the inventor's contribution and that the level of knowledge and skill in the art would not allow one skilled in the art to recognize that applicant was in possession of the claimed genus consistent with the cited written description guidelines for the reasons outlined in the above rejection. When there is little to no disclosure in the instant specification of the starting material or conditions under which claimed process can be carried out, as in this case (see rejection above), this failure cannot be rectified by asserting that all disclosure related to the process is within skill of art. *Genentech Inc. v. Novo Nordisk A/S* (CA FC) 42 USPQ2d 1001 (3/13/1997).

[2] To the extent that Applicants are simply reiterating their previous arguments, the Examiner contends that those points were adequately addressed in the previous office actions, which are incorporated in their entirety herein by reference. In addition, the Examiner notes that the "level of skill and knowledge in the art, partial structure, physical and/or chemical properties ... etc." show that Applicants were not in possession of the "full scope" of the claimed invention. For example, in response to Applicant's argument that the claims are limited to "a unique family

of restriction endonucleases that excise a fragment containing the recognition site", it is noted that the features upon which applicant relies (i.e., a "unique family of restriction enzymes") is not recited in the rejected claim(s). In addition, the specification does not make explicit statements that only "double cleavage" enzymes can be employed, nor does it define any other "unique family" of restriction enzymes that can be used. For example, in *Johnson Worldwide Associates v. Zebco Corp.* 175 F.3d 985, 993, 50 USPQ2d 1607, 1613 (Fed. Cir. 1999) the court stated, "the court's determination [in *Gentry Gallery*] that the patent disclosure did not support a broad meaning for the disputed claim terms was premised on clear statements in the written description that described the location of a claim element--the 'control means'--as 'the only possible location' and that variations were 'outside the stated purpose of the invention.' Gentry Gallery, 134 F.3d at 1479, 45 USPQ2d at 1503. Gentry Gallery, then, considers the situation where the patent's disclosure makes crystal clear that a particular (i.e., narrow) understanding of a claim term is an 'essential element of [the inventor's] invention.'" No such "crystal clear" statements are present in the present application, in contrast to *Gentry Gallery*, that might otherwise limit the currently claimed restriction enzymes to a particular undefined "unique" class. Thus, Applicants' claims read on "any" restriction enzyme that can be used either by changing the enzyme's substrate specificity via altering the reaction conditions (e.g., George et al., see above) or mutation (e.g., Lanio et al., see above) or by employing various "single cleavage" enzymes that cut outside the recognition site (e.g., FokI). This is further supported by Applicants' claim construction wherein dependent claims like 38 further limit the generic claim to dual cleavage restriction enzyme sites, which implies that the broader generic claim includes "single cleavage" enzymes. Furthermore, the Examiner is unaware of any art-recognized

"unique class" of restriction enzymes that include both "single" and "double" cleavage enzymes. In addition, the Examiner notes that claims are to be given their broadest reasonable interpretation consistent with Applicants' specification (e.g., see *In re Zletz*, 13 USPQ2d 1320, 1322 (Fed Cir. 1989) (holding that claims must be interpreted as broadly as their terms reasonably allow); MPEP § 2111. Although, "double cleavage" restriction sites are set forth as a "preferred embodiment" and "BaeI" is the only enzyme listed, nothing in the specification expressly states that these "double cleavage" enzymes are "critical" to the performance of the invention.

The Examiner also notes that the written description factors cited by Applicants (e.g., level of skill and knowledge in the art, partial structure, physical and/or chemical properties, etc.) all favor a finding for a lack of written description. For example, Applicants have not provided a structure for a "single cleavage" restriction/snRNA construct (Applicants only provide the "dual cleavage" BaeI/snRNA). In addition, no physical and/or chemical properties are provided that might otherwise allow a person of skill in the art to identify such a construct. In fact, a vector containing one "single cleavage" recognition site could not even provide a fragment without performing some addition undefined method steps. Likewise a restriction enzyme that cleaves inside its own recognition site could not provide a restriction fragment that excises its own intact recognition site without performing some unspecified genetic alteration of the restriction enzyme and/or tweaking of the reaction conditions. In addition, no structure/activity relationship is set forth, no method steps are provided for making the "single cleavage" recognition site.

[3] The Examiner has withdrawn the 112, second paragraph rejection with regard to "restriction site" in view of Applicants' amendments (e.g., see above). However, this does not change a finding for a lack of written description as outlined above.

Accordingly, the written description rejection cited above is hereby maintained.

New Rejections and/or Objections

Objections to the Claims

7. Claims 49 and 50 are objected to because of the following informalities:

A. Claims 49 and 50 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form or rewrite the claim(s) in independent form. Claim 49 depends from claim 47. Claim 47 was canceled. Therefore, claim 49 (and also claim 50) cannot further limit this claim.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. Claims 32-34 and 41 are rejected under 35 U.S.C. 102(a) as being anticipated by Vidaver et al. (Vidaver, R. M.; Fortner, D. M.; Loos-Austin, L. S.; Brow, D. A. "Multiple Functions of

Saccharmocyes cerevisiae Splicing Protein Prp24 in U6 RNA Structural Rearrangments"

Genetics, **November 1999**, *153*, 1205-1218).

For ***claim 32 and 41***, Vidaver et al. (see entire document) disclose the recombinant snRNA vector pSE358-snr6-A62G,U89C (e.g., see Vidaver et al., page 1207, column 1, paragraph 1), which anticipates the claimed invention. For example, Vidaver et al. disclose a recombinant vector comprising the U6 snRNA (see above). In addition, Vidaver et al. disclose a modified nucleotide sequence (i.e., the PCR product that has been cut with EcoNI and BstBI just before its incorporation into thepSE358-snr6-A62G,U89C vector), which has been modified to contain one or more recognition sites (i.e., FokI recognition site) such that digestion with a single restriction enzyme (i.e., FokI) will excise a restriction fragment from the modified nucleotide sequence (i.e., the "nucleotide sequence" that has "not yet been cloned" into the vector, see note below). which includes said recognition site and forms insertion sites in said nucleotide sequence Although the reference doesn't explicitly state that digestion with a single FokI enzyme would excise a single restriction fragment that contains the recognition sequence, the Examiner contends that this limitation would be inherently disclosed by Vidaver et al. as FokI cleaves nine bases away (i.e., GGATG$(N)_9$^) from its recognition site, which would leave the recognition site intact. Furthermore, Vidaver et al. has already shown that this FokI site can be used for "insertions" as the PCR product of the U6-U89C reaction was ligated into it. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The

Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). Please note that the claimed "restriction fragment" need not be "excised" from "the vector" (e.g., claim 32 doesn't read "… such that digestion with a single restriction enzyme excises a restriction fragment which includes said recognition site and forms insertions sites in said vector") but, rather, only requires the restriction fragment to be excised from "said nucleotide sequence [i.e., the sequence that subsequently gets incorporated into said vector]" (e.g., see claim 32). Thus, a fragment that would be produced from the digestion of an "unincorporated" nucleotide sequence meets all of the currently claimed limitations.

For ***claims 33 and 34***, Vidaver et al. disclose U6 snRNA (e.g., see abstract; see also page 1207, column 1, paragraph 1).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claim 32-34, 41, 42, 44-46, 48 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noonberg et al. (WO 95/10607) (Date of Patent is **April 20, 1995**) (of record) in view of Cease et al. (Cease, K. B.; Cortland, J. L. "A vector for facile PCR product cloning and modification generating any desired 4-base 5' overhang: pRPM" *Biotechniques* **1993**, *14(2)*, 250-5).

For ***claims 32 and 42***, Noonberg et al. (see entire document) disclose ribozyme oligonucleotide constructs (e.g., see Noonberg et al., abstract), which reads on the claimed invention. For example, Noonberg et al. disclose a recombinant vector comprising an isolated nucleotide sequence encoding a snRNA (e.g., U6), wherein said nucleotide sequence [i.e., vector] has been modified to contain one or more restriction sites [i.e., SmaI], such that digestion with at least one restriction enzyme excises a restriction fragment [i.e., U6] and forms insertion sites in said nucleotide sequence for cloning (e.g., see Example 3, "The human U6 gene [snRNA] cloned within the SmaI site of pGem1 [recombinant vector]"; see also page 56, paragraph 2; see also claim 24; see also page 9, lines 9-10). In addition, Noonberg et al. disclose "two insertion sites" (i.e., the 3' and 5' blunt ends of the SmaI linearized pGem1), which are formed by the

digestion of a single SmaI endonuclease. In this scenario, the library of U6 represent the "cassette" (e.g., see figures 4B and 9 wherein a U6 snRNA vector is shown that has XhoI and NsiI restriction sites for inserting synthetic sequences; see also page 25, paragraph 2; see also page 36, paragraph 2; see also page 41, last paragraph; see especially page 50; see also page 56, paragraph 2; see also claim 24; see also page 9, lines 9-10; see also page 35, paragraph 1, "The oligonucleotides can be designed for binding to different regions of different DNA or RNA targets, to different regions of the same DNA or RNA target, or to the same region of the same DNA or RNA target. Decisions as to vector design would be based upon whether the experimenter wanted to hit multiple targets broadly or a single target intensely"; see also figure 2(a) wherein the insertion of multiple oligos [i.e., a cassette] are shown; see also page 6, line 10; see also page 8, line 1; see also page 10, line 18; see also page 15, first full paragraph; see also page 38, line 31; see also page 39, lines 8-13; see also page 40, last paragraph; see also page 43, last paragraph; see also page 49, Example 2; see also page 2, Antisense section).

For ***claims 33, 34, 44 and 45***, Noonberg et al. disclose, for example, U6 snRNAs (e.g., see figure 4; see also page 50, Example 3; see also page 38, line 10; see also figures 19-21; see also pages 22-23; see also page 87, paragraph 2-3; see also page 93, last paragraph).

For ***claim 48***, Noonberg et al. disclose any restriction site including XhoI, NsiI wherein the restriction sites are excised to produce a double stranded insert (e.g., see page 33, paragraph 2, "Of course the XhoI and NsiI restriction sites can be replaced with ***any***

first and second unique restriction enzyme sites to facilitate insertion of the specific nucleotide sequence").

For ***claim 41 and 51***, Noonberg et al. disclose overhanging ends that are complementary (e.g., see page 51, line 7).

For ***claim 46***, Noonberg et al. disclose 30 bp insert (e.g., see page 50, Example 3 wherein insert is U6 gene from +25 to +55, which is 30 bp long).

The prior art teachings of Noonberg et al. differ from the claimed invention as follows:

For ***claims 32 and 42***, Noonberg et al. fail to disclose a modified nucleotide sequence that upon digestion with a single restriction enzyme would excise a restriction fragment that includes the recognition site. Noonberg et al. only disclose the use of SmaI, which would destroy the recognition site (i.e., cleavage is CCC↓GGG).

For claim 37, Noonberg et al. fail to teach the use of two identical recognition sites.

However, Cease et al. teach the following limitations that are deficient in Noonberg et al.:

For ***claims 32 and 42***, Cease et al. (see entire document) teach the use of classIIs restriction recognition sites such as FokI and BbsI in a vector for facile PCR cloning, (e.g., see abstract), which upon cleavage by either enzyme produce a restriction fragment that contains the restriction site (e.g., see figure 2, step 4 wherein said fragment is the BbsI cut pRPM).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the pRPM vectors disclosed by Cease et al. to clone the U6 gene disclosed by Noonberg et al. because Noonberg et al. explicitly state that their plasmids have broad utility for all cloning applications (e.g., see Cease et al., abstract, "These 'reach-over' product modification vectors represent general and flexible tools for the generation of fragments for use in engineering DNA constructs"; see also Introduction, "We sought a general method for the generation of DNA fragments … of any desired sequence, in the reading frame of choice, without the addition of an extraneous sequence"). Furthermore, a person of skill in the art would have been motivated to use the pRPM constructs disclosed by Cease et al. because according to Cease et al., page 189, column 1, last full paragraph, "The plasmids pRPM1 and PRPM2 represent powerful and general tools for the cloning and modification of PCR-amplified DNA by yielding an r-base 5' overhangs of choice. As, such they can enable or simplify many strategies and tactics in the development of DNA constructs"; see also column 1, paragraphs 2 and 3; see also abstract). In addition, a person of skill in the art would reasonably have expected to be successful because Cease et al. state, ""These 'reach-over product modification vectors represent general and flexible tools for the generation of fragments for use in engineering DNA construct" (e.g., see abstract) and thus possess broad utility. In addition, Cease et al. show the use of SmaI cleavage sites in the pRPM1 construct, which is exactly the same SmaI cleavage site shown to be useful for the construction of the U6/pGem1 in the Cease et al. reference.

12. Claims 32-35, 41-46, 48 and 51 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Noonberg et al. (WO 95/10607) (Date of Patent is April 20, 1995) (of record) and Cease et al. (Cease, K. B.; Cortland, J. L. "A vector for facile PCR product cloning and modification generating any desired 4-base 5' overhang: pRPM" *Biotechniques* **1993**, *14(2)*, 250-5) and the admission of prior art in the specification and Cohen et al. (Cohen, J. B.; Snow, J. E.; Spencer, S. D.; Levinson, A. D. "Suppression of mammalian 5' splice-site defects by U1 small nuclear RNAs from a distance" PNAS 1994, 91, 10470-10474) (see IDS 3, reference AT) and Tuschl et al. (Tuschl, T.; Sharp, P. A.; Bartel, D. P. "Selection in vitro of novel ribozymes from a partially randomized U2 and U5 snRNA library" EMBO 1998, 17, 9, 3637-2650) (of record).

For ***claims 32-34, 41, 42, 44-46, 48 and 51***, the combined references of Noonberg et al. and Cease et al. teach all the limitation stated in the 35 U.S.C. § 103(a) rejection above (incorporated in its entirety herein by reference), which renders obvious claims 32-34, 41, 42, 44-46, 48 and 51.

The prior combined references of Noonberg et al. and Cease et al. differ from the claimed invention as follows:

For ***claims 35 and 43***, the combined references of Noonberg et al. and Cease et al. are deficient in that it does not specifically teach the use of U1 snRNA recombinant vector or U1 snRNA recombinant vector with insertion cassette wherein the sequence has been modified within the first 11 nucleotides of the coding region.

However, the admission in the specification and the Cohen et al. and Tuschl et al. references teach the following limitations that are deficient in the combined references of Noonberg et al. and Cease et al.:

For ***claims 35 and 43***, Tuschl et al. (see entire document) disclose a recombinant vector encoding U2 and U6 snRNA with a 40-nucleotide insertion cassette contained between two insertion sites (e.g., see Tuschl et al., figures 1-2, see also Materials and Methods, Pool Construction, selection and amplification). Furthermore, the admission in the specification combined with the reference that the specification refers to (i.e., the Noonberg et al. reference) teach that a person of skill in the art would recognize the value of using any U snRNA including U1 snRNA extending the teachings of Tuschl et al. from U2/U6 to U1 snRNA (e.g., see specification, Background of the Invention, pae 1, last paragraph, "There has long bee interest in utilizing the various splicing functions of individual U snRNA to inhibit or modify transcription, and, thereby, to suppress undesired expression products (Cohen, et al., 1994, PNAS 91: 10470-10474) [which specifically cites the use of U1 snRNA, see entire document, especially abstract and Materials and Methods section]). Such suppression has enormous therapeutic potential"). Furthermore, Cohen et al. teach a modification within the first 11 nucleotides (e.g., see Figure 3 A, U1-αA5 which has a mutation in the "fifth" position which is within the first eleven nucleotides).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to make a recombinant vector encoding snRNA with an insertion cassette as taught by the combined references of Noonberg et al. and Cease et al. with the

U1 snRNA cassette vector as taught by the admission in the specification, Cohen et al. and Tuschl et al. references because the admission in the specification sates that any U snRNA would be a candidate for recombinant technology and specifically point to U1 snRNA by citing the Cohen et al. reference (e.g., see specification, page 1, last paragraph; see also Cohen et al., entire document). Furthermore, one of ordinary skill in the art would have been motivated to use the U1 snRNA as taught by the admission in the specification and Cohen et al. because according to the specification modification of such a snRNA would have "enormous therapeutic potential" and specifically recites a reference (i.e., the Cohen et al. reference) that addresses the use of U1 snRNA. In addition, Noonberg et al. teach that their invention is "an improved method" for the delivery of ribozymes (e.g., see Noonberg et al., page 1, line 24; see also page 14, line 27; see especially page 24, last paragraph), which would encompass the ribozymes disclosed by Cohen et al. and Tuschl et al. Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because all the references teach that recombinant U snRNAs can be made into a vector and mutated. In addition, Noonberg et al. states, "… any oligonucleotide that is desired to be transcribed within the cell [can be used] … including … a ribozyme" (e.g., see paragraph bridging pages 29-30), which specifically points toward the ribozyme papers of Cohen et al. and Tuschl et al. Furthermore, Noonberg et al. states that the advantages of using their invention with ribozymes like those disclosed by Cohen et al. and Tuschl et al. are that "RNA polymerase III transcribes at a nearly constant rate and high frequency in almost all mammalian cell types … [and]

are also highly efficient allowing for clean transcription" (e.g., see Cohen et al., page 36, first full paragraph).

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
January 6, 2006

ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600